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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/036,645	BERD, DAVID	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 21-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 21-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 18, 2005. Claims 1-2 and 21-33 are pending. Claims 32 and 33 were added in the response of November 18, 2005. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Improper Amendment

2. The amendment filed November 18, 2005 does not comply with the requirements of 37 CFR 1.173(b), which sets forth the manner of making amendments in reissue applications. The amendment does not comply with 37 CRF 1.173(b)(2) because the complete content of each of the newly added claims 21-33 (i.e., the claims that were not presented in the patent) is not underlined.

Additionally, the amendment includes text with strikethroughs. However, in a reissue application, all information in the claims that is to be omitted must be enclosed in brackets. Also, the status of the claims should be listed as "amended," "twice amended" etc, rather than "currently amended."

Oath/Declaration

3. The reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant. See 37 CFR 1.175 and MPEP § 1414.

A new reissue declaration was filed on November 18, 2005. This declaration includes a statement that "All errors in this reissue application, up to the time of the filling of this reissue application, arose without any deceptive intention on the part of the applicants." However, the new reissue declaration does not include the required statement that "all errors being corrected in the reissue application up to the time of filing of the oath or declaration arose without any deceptive intention on the part of the applicant." See 37 CRF 1.175(a)(2).

4. Claims 1-2 and 21-33 are rejected as being based upon a defective reissue oath/declaration under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175. The nature of the defect(s) in the oath/declaration is set forth in the discussion above in this Office action.

Claim Rejections - 35 USC § 103

5.The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (Proceedings of the American Association for Cancer Research. March 1989. 30: page 382, abstract #1515) in view of Berd (Cancer Investigation. 1988. 6(3): 337-349; previously cited in IDS of U.S. Patent No. 5,290,551).

Berd (1989) teaches that treatment of melanoma patients with cyclophosphamide (CY) followed by autologous vaccine induces delayed-type hypersensitivity to

melanoma cells and in some cases regression of metastatic cancer. To enhance this treatment, Berd studied the effectiveness of administering hapten conjugated autologous melanoma cells. The method of Berd comprises: (i) administering to a patient a low dose of cyclophosphamide; and (ii) 3 days following treatment with CY, injecting patients with a vaccine containing 10-25 x 10^6 autologous, irradiated melanoma cells mixed with Bacille Calmette-Guerin(BCG). Berd reports that in a study of melanoma patients, one patient developed erythema and swelling in the dermal metastases on her leg and lower abdomen, followed by ulceration and drainage of necrotic material and some level of regression of the metastases. A second patient also showed erythema and swelling of the skin of her lower abdomen and groin and a change in consistency from rock-hard tumor to fluctuant. A third patient exhibited moderate erythema. All 3 patients developed delayed-type hypersensitivity (DTH) against both DNCB and DNP-conjugated autologous lymphocytes. Berd concluded that "(a)lthough the results are preliminary, they suggest that this new strategy may represent a significant advance in the immunotherapy of human melanoma."

While Berd (1989) teaches that the patients were injected with the DNP-conjugated melanoma vaccine, Berd does not specifically teach that the injection was intradermal, or that the injection was made to 3 sites on an upper arm or leg.

However, Berd (1988) teaches methods of immunotherapy for human melanoma wherein 10-25 x 10^6 autologous melanoma cells mixed with BCG are injected intradermally into three sites on the patients upper arm or legs (see page 340, column 1). Berd reports that patients receiving CY and the melanoma vaccine developed DTH

to tumor antigens (page 342, column 2). Three of the patients tested showed complete remission, one partial remission and two had minor responses to the vaccine (page 344, column 2).

According, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Berd (1989) by injecting the DPN-conjugated melanoma vaccine mixed with BCG intradermally to 3 contiguous sites on the patient's upper arm or leg because as taught by Berd (1988) this is a conventional means for administering the melanoma cancer vaccine and would have provided an effective route of administration.

With respect to the recitation in the claims of "wherein administration of said vaccine induces a delayed-type hypersensitivity (DTH) response against unmodified melanoma cells" it is considered to be a property of the vaccine of Berd that it is capable of inducing a DTH response against unmodified melanoma cells. Given that the vaccine of Berd is identical to the vaccine of the present invention, in the absence of evidence to the contrary, the vaccine of Berd (1989) is expected to function similarly to the present vaccine. Therefore, the resulting method of intradermally injecting the DNP-vaccine of Berd (1989) would have necessarily resulted in a DTH response against unmodified melanoma cells.

With respect to claims 28 and 29, Berd (1989) does not characterize the melanoma patients that were treated with the DNP-conjugated melanoma vaccine and thereby does not specifically teach administering the vaccine to post-surgical melanoma patients or to stage 4 melanoma patients. However, Berd (1988; see, e.g., page 340)

teaches administering melanoma vaccines to patients post-surgically and to patients with extensive metastatic disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered the DNP- conjugated melanoma vaccine of Berd (1989) to patients post-surgically and to stage 4 melanoma patients in order to have provided an effective means of treatment for those patients most in need of therapy.

With respect to claim 30, Berd (1989) teaches that of the four patients studied, three "developed a striking inflammatory response in tumor masses after 2 vaccine treatments (8 weeks)." Further, Berd (1988; page 340) teaches repeating the vaccine treatment every 28 days. The number of vaccine treatments ranged from 1 to 15, with a median of 4 treatments. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have intradermally administered the DNP-conjugated melanoma vaccine every 4 weeks because this would have boosted the response to the vaccine and thereby would have increased the effectiveness of the therapy.

With respect to claim 31, Berd (1989) does not teach that the autologous melanoma cells are cryopreserved. However, Berd (1988; page 340) teaches that the tumor masses are removed from the patient and tumor cells are cryopreserved in liquid nitrogen until needed. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used cryopreserved autologous melanoma cells because this would have provided a more convenient means of

administering the therapy since such cells could be frozen and stored and then administered at 4 week intervals.

6. Claims 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (Proceedings of the American Association for Cancer Research. March 1990. 31: page 279, abstract #1654) in view of Berd (1988).

Berd (1990) teaches a method of treating metastatic melanoma wherein the method comprises: (i) administering to a melanoma patient a low dose of cyclophosphamide; and (ii) 3 days following treatment with CY, injecting patients with a vaccine containing 10-25 x 10^6 autologous, irradiated melanoma cells. Berd reports that the vaccine induced a "striking inflammatory response in 11/15 patients, consisting of erythema, swelling, warmth and tenderness around tumor masses." Further, 92% of the patients developed DTH to the DNP-conjugated melanoma cells. The reference states that the "DNP-vaccine seems to induce a degree of anti-melanoma immunity not seen with previously tested immunotherapy."

While Berd (1990) teaches that the patients were injected with the DNP-conjugated melanoma vaccine, Berd does not specifically teach that the injection was intradermal, or that the injection was made to 3 sites on an upper arm or leg.

However, Berd (1988) teaches methods of immunotherapy for human melanoma wherein 10-25 x 10^6 autologous melanoma cells mixed with BCG are injected intradermally into the three sites on the patients upper arm or legs (see page 340, column 1). Berd (1988) reports that patients receiving CY and the melanoma vaccine developed DTH to tumor antigens (page 342, column 2). Three of the patients tested

showed complete remission, one partial remission and two had minor responses to the vaccine (page 344, column 2).

According, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Berd (1990) by injecting the DPN-conjugated melanoma vaccine mixed with BCG intradermally to 3 contiguous sites on the patient's upper arm or leg because as taught by Berd (1988) this is a conventional means for administering the melanoma cancer vaccine and would have provided an effective route of administration.

With respect to the recitation in the claims of "wherein administration of said vaccine induces a delayed-type hypersensitivity (DTH) response against unmodified melanoma cells" it is considered to be a property of the vaccine of Berd that it is capable of inducing a DTH response against unmodified melanoma cells. Given that the vaccine of Berd is identical to the vaccine of the present invention, in the absence of evidence to the contrary, the vaccine of Berd (1990) is expected to function similarly to the present vaccine. Therefore, the resulting method of intradermally injecting the DNP-vaccine of Berd (1990) would have necessarily resulted in a DTH response against unmodified melanoma cells.

Further, Berd (1990) does not teach that the vaccine is mixed with BCG. However, Berd (1988; page 340) teaches mixing the melanoma vaccine with the immunological adjuvant BCG. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have mixed the DNP-

conjugated melanoma vaccine with the immunological adjuvant BCG in order to have further enhanced the patient's immune response.

With respect to claims 28 and 29, Berd (1990) does not characterize the melanoma patients that were treated with the DNP-conjugated melanoma vaccine and thereby does not specifically teach administering the vaccine to post-surgical melanoma patients or to stage 4 melanoma patients. However, Berd (1988; see, e.g., page 340) teaches administering the melanoma vaccine to patients post-surgically and to patients with extensive metastatic disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered the DNP- conjugated melanoma vaccine of Berd (1990) to patients post-surgically and to stage 4 melanoma patients in order to have provided an effective means of treatment for those patients most in need of therapy.

With respect to claim 30, Berd (1990) teaches that patients were injected with the DNP-conjugated melanoma vaccine every 4 weeks.

With respect to claim 31, Berd (1990) does not teach that the autologous melanoma cells are cryopreserved. However, Berd (1988; page 340) teaches that the tumor masses are removed from the patient and tumor cells are cryopreserved in liquid nitrogen until needed. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used cryopreserved autologous melanoma cells because this would have provided a more convenient means of administering the therapy since such cells could be frozen and stored and then administered at 4 week intervals.

7. Claims 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al (Laboratory Investigation. 1990. 62(1): 70A, abstract #412) in view of Berd (1988).

Murphy teaches a method of treating metastatic melanoma wherein the method comprises: (i) administering to a melanoma patient a low dose of cyclophosphamide; and (ii) 3 days following treatment with CY, injecting patients with a vaccine containing 10-25 x 10^6 autologous, irradiated melanoma cells mixed with Bacille Calmette-Guerin(BCG). Murphy reports that 7 patients showed clinical regression following treatment.

While Murphy teaches that the patients were injected with the DNP-conjugated melanoma vaccine, Murphy does not specifically teach that the injection was intradermal, or that the injection was made to 3 sites on an upper arm or leg.

However, Berd (1988) teaches methods of immunotherapy for human melanoma wherein 10-25 x 10^6 autologous melanoma cells mixed with BCG are injected intradermally into the three sites on the patients upper arm or legs (see page 340, column 1). Berd (1988) reports that patients receiving CY and the melanoma vaccine developed DTH to tumor antigens (page 342, column 2). Three of the patients tested showed complete remission, one partial remission and two had minor responses to the vaccine (page 344, column 2).

According, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Murphy by injecting the DPN-conjugated melanoma vaccine mixed with BCG intradermally to 3 contiguous sites

on the patient's upper arm or leg because as taught by Berd (1988) this is a conventional means for administering the melanoma cancer vaccine and would have provided an effective route of administration.

With respect to the recitation in the claims of "wherein administration of said vaccine induces a delayed-type hypersensitivity (DTH) response against unmodified melanoma cells" it is considered to be a property of the vaccine of Berd that it is capable of inducing a DTH response against unmodified melanoma cells. Given that the vaccine of Murphy is identical to the vaccine of the present invention, in the absence of evidence to the contrary, the vaccine of Murphy is expected to function similarly to the present vaccine. Therefore, the resulting method of intradermally injecting the DNP-vaccine of Murphy would have necessarily resulted in a DTH response against unmodified melanoma cells.

With respect to claims 28 and 29, Murphy does not characterize the melanoma patients that were treated with the DNP-conjugated melanoma vaccine and thereby does not specifically teach administering the vaccine to post-surgical melanoma patients or to stage 4 melanoma patients. However, Berd (1988; see, e.g., page 340) teaches administering the melanoma vaccine to patients post-surgically and to patients with extensive metastatic disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered the DNP- conjugated melanoma vaccine of Murphy to patients post-surgically and to stage 4 melanoma patients in order to have provided an effective means of treatment for those patients most in need of therapy.

With respect to claim 30, Murphy does not specifically teach that patients were injected with the DNP-conjugated melanoma vaccine every 4 weeks. However, Berd (1988a; page 340) teaches repeating the vaccine treatment every 28 days. The number of vaccine treatments ranged from 1 to 15, with a median of 4 treatments. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have intradermally administered the DNP-conjugated melanoma vaccine every 4 weeks because this would have boosted the response to the vaccine and thereby would have increased the effectiveness of the therapy.

With respect to claim 31, Murphy does not teach that the autologous melanoma cells are cryopreserved. However, Berd (1988; page 340) teaches that the tumor masses are removed from the patient and tumor cells are cryopreserved in liquid nitrogen until needed. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used cryopreserved autologous melanoma cells because this would have provided a more convenient means of administering the therapy since such cells could be frozen and stored and then administered at 4 week intervals.

8. Claims 2 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (1989) in view of Berd (1988), as applied to claims 26-31 above, and further in view of Fujiwara (The Journal of Immunology. 1980. 124: 863-869).

The teachings of Berd (1989) and Berd (1988) are presented above. Berd (1989) teaches treating melanoma patients with a hapten conjugated melanoma vaccine, wherein the hapten is dinitrophenyl (DNP). Berd (1989) does not teach treating

melanoma patients with a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Berd (1989) so as to have used TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

9. Claims 2 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (1990) in view of Berd (1988), as applied to claims 26-31 above, and further in view of Fujiwara.

The teachings of Berd (1990) and Berd (1988) are presented above. Berd (1990). Berd (1990) does not teach treating melanoma patients with a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Berd (1990) so as to have used TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

10. Claims 2 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Berd (1988), as applied to claims 26-31 above, and further in view of Fujiwara.

The teachings of Murphy and Berd (1988) are presented above. Murphy teaches treating melanoma patients with a hapten conjugated melanoma vaccine, wherein the hapten is dinitrophenyl (DNP). Murphy does not teach treating melanoma patients with a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murphy so as to have used TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

11. Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (1989) and Fujiwara.

The teachings of Berd (1989) are presented above. Berd (1989) teaches using a hapten conjugated melanoma vaccine to treat melanoma patients, wherein the hapten is dinitrophenyl (DNP). Berd (1989) does not teach a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Berd (1989) so as to have used TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

With respect to newly added claim 32, Berd teaches that the hapten-conjugated vaccine is administered with BCG, which is considered to be an immunomodulating drug, since BCG stimulates the immune response. It is noted that the claims do not

require that the immunomodulating agent is distinct from the immunological adjuvant, and therefore the present claims include vaccines comprising BCG which acts as an immunological adjuvant and immunomodulating drug.

12. Claim 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd et al (1990) and Berd (1998) in view of Fujiwara.

The teachings of Berd are presented above. In particular, Berd (1990) teaches using a hapten conjugated melanoma vaccine to treat melanoma patients, wherein the hapten is dinitrophenyl (DNP). Berd (1990) does not teach a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Berd (1990) so as to have used

TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

With respect to newly added claim 32, Berd (1988) teaches administering the hapten-conjugated vaccine to enhance the patient's immune response. BCG is considered to be an immunomodulating drug, since BCG stimulates the immune response. It is also noted that the claims do not require that the immunomodulating agent is distinct from the immunological adjuvant, and therefore the present claims include vaccines comprising BCG which acts as an immunological adjuvant and immunomodulating drug.

13. Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Fujiwara.

The teachings of Murphy are presented above. Murphy teaches using a hapten conjugated melanoma vaccine mixed with BCG to treat melanoma patients, wherein the hapten is dinitrophenyl (DNP). Murphy does not teach a hapten conjugated melanoma vaccine wherein the hapten is trinitrophenyl (TNP).

Fujiwara (page 864) teaches conjugating TNP to tumor cells and the use of TNP-conjugated tumor cells to treat tumors. The reference teaches that the TNP-conjugated tumor cells induced enhanced tumor-specific immunity leading to regression of growing tumor when administered following priming with TNP (see abstract and page 868). Fujiwara teaches that the augmented immunity is due to the activity of cytotoxic T cells and T cells essential for tumor rejection.

In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, the ordinary artisan would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to provide an effective means for treating melanoma. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murphy so as to have used TNP in place of DNP as the hapten in order to have provided an equally effective vaccine for treating melanoma.

With respect to newly added claim 32, Murphy teaches that the hapten-conjugated vaccine is administered with BCG, which is considered to be an immunomodulating drug, since BCG stimulates the immune response. It is noted that the claims do not require that the immunomodulating agent is distinct from the immunological adjuvant, and therefore the present claims include vaccines comprising BCG which acts as an immunological adjuvant and immunomodulating drug.

14. **RESPONSE TO ARGUMENTS:**

Rejections under 35 U.S.C. 103 of claims 26-31 as unpatentable over Berd (1989) in view of Berd (1988), Berd (1990) in view of Berd (1988), and Murphy (1990) in view of Berd (1988).

In the response of November 18, 2005, Applicants argue that Berd (1989), Berd (1990) and Murphy (1990) are each directed to methods of treating melanoma using haptenized tumor cells as a vaccine, whereas Berd (1988) is directed to methods of

treating melanoma using non-haptenized tumor cells as a vaccine. Applicants argue that there is no suggestion that the haptenized cells would work in combination with the method of Berd (1988).

Applicants arguments have been fully considered but are not persuasive. The disclosed methods of Berd (1989), Berd (1990) and Murphy (1990) differ from the claimed invention in that they do not specify the location at which the vaccine is injected into the patient, and particularly do not specify injection of the vaccine intradermally at 3 sites on the patients upper arm or leg. However, injection of vaccines intradermally at 3 sites on the patients upper arm or leg was conventional in the art at the time the invention was made. Berd (1988) was cited for teaching this route of administration of vaccines for the treatment of melanoma. The skilled artisan would have clearly recognized that the teachings of Berd (1988) regarding the administration of non-haptenized vaccines would also be applicable to haptenized vaccines given the conventionality of this route of administration of vaccines, particularly for the treatment of melanoma. Applicants have not shown any unexpected results associated with administering the haptenized vaccine intradermally at 3 sites on the patients upper arm or leg and have not provided any sound scientific arguments to support their contention that the teachings of Berd regarding the route of administration of vaccines would not be applicable to haptenized vaccines. Accordingly, it is maintained that the combined references provide both the motivation and more than a reasonable expectation of success of treating melanoma patients by administering the haptenized vaccines of

Berd (1989 and 1990) and Murphy (1990) intradermally at 3 sites on the patients upper arm or leg.

Rejections under 35 U.S.C. 103 of claims 2 and 21-25 as unpatentable over Berd (1989) in view of Berd (1988) and Fujiwara, and over Berd (1990) in view of Berd (1988) and Fujiwara

Applicants traverse the 35 U.S.C. 103 rejections of claims 2 and 21-25 over Berd (1989) in view of Berd (1988) and Fujiwara and over Berd (1990) in view of Berd (1988) and Fujiwara by stating that there is no motivation to combine the stated references and there is no expectation of success in treatment of melanoma with a TNP-modified vaccine. Applicants assert that Berd 1988, 1989 and 1990 disclose methods of treating melanoma using DNP-modified human melanoma cells, while Fujiwara relates only to TNP-modified mouse leukemia or plastmacytoma cells.

Applicant's argument have been fully considered but are not persuasive. While Fujiwara exemplifies methods of vaccination using TNP-conjugated tumor cells to treat mouse leukemia or plastmacytoma cells, the teachings of Fujiwara are not in fact limited to only the treatment of these two types of cancer. Rather, Fujiwara teaches, in general, that TNP-conjugated tumor cells generate an immune response and enhance the rejection of tumor cells. Fujiwara (abstract) states "The magnitude of tumor-neutralizing activity developed in the presence of TNP-amplifier system was as much as 20-fold greater than for control, and this augmented tumor-neutralizing activity was also tumor specific and T cell mediated. Thus, the present system provides an effective manipulation for eliciting enhanced in vivo tumor rejection as well as in vigor cytotoxic

response, and illustrates a role of amplifier T cells in augmentation of syngeneic tumor immunity."

Applicants also traverse this rejection by stating that the method of Fujiwara includes a step of priming by administering TNP modified proteins in order to elicit a stronger response, but that the methods of Berd (1988, 1989 and 1990) do not require this priming step. This argument is not persuasive because the claims do not exclude including a priming step with TNP modified proteins. Further, Fujiwara teaches including the priming step only to further improve the immune response, but is not mandatory. Additionally, Berd (1989 and 1990) do in fact include a priming step with the hapten in which patients are sensitized to DNP by topical administration of dinitrochlorobenzene prior to administering the hapten-conjugated vaccine.

In view of the high level of structural similarity between the DNP and TNP haptens, the ordinary artisan would have expected that TNP could be used in place of DNP and would be equally effective at enhancing the immune response. It is noted that the present specification does not provide any data for TNP-conjugated melanoma vaccines or AED-conjugated melanoma vaccines. The teachings in the specification regarding TNP and AED are limited to a single sentence of: "Other useful haptens include TNP and AED which may be chemically linked to the tumor cells" (see column 3, lines 58-59 of '551). In addressing the enablement of the present invention, Applicants previously argued in the March 6, 1992 response of '551 that "Other haptens of the claimed invention, trinitrophenyl and N-iodoacetyl-N'-(5 sulfonic 1-naphthyl) ethylene diamine, would be expected to behave similarly to DNP" and conclude that the

selection and use of alternative haptens, such as TNP, would have been well within the skill of the art. The specification has not established any unexpected results associated with the use of TNP and has acknowledged the obviousness of using alternative haptens with the expectation that they will behave similarly to DNP. Moreover, obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). Thereby, the claimed invention would have been obvious to and well within the ordinary skill of the art at the time the invention was made. Accordingly, the ordinary artisan also recognizing the similarity in structure between DNP and TNP and appraised of the teachings of Fujiwara of the use of TNP as a hapten to augment the immune response to tumors, would have been motivated to have used, and would have had more than a reasonable expectation of success at using TNP-conjugated melanoma vaccines for the treatment of melanoma.

Therefore, the rejections are maintained because the combined references when considered as a whole provide both the motivation and a reasonable expectation of success of using TNP-conjugated melanoma vaccines in place of DNP-conjugated melanoma vaccines for the treatment of cancer.

Rejections under 35 U.S.C. 103 of claims 2 and 21-25 as unpatentable over Murphy (1990) in view of Berd (1988) and Fujiwara

Applicants traverse this rejection by stating that neither Murphy nor Berd teach the use of TNP or AED-modified tumor cells and therefore the combined references do

not teach each of the limitations recited in the claims. However, the rejection is based on the combined teaches of Murphy (1990), Berd (1988) and Fujiwara. As set forth in the rejection, Fujiwara teaches the use of TNP-modified tumor cells as a vaccine. In view of the teachings of Fujiwara of the effectiveness of TNP-conjugated tumor cells to augment immunity and enhance the tumor rejection response and in view of the known structural similarities between DNP and TNP, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used TNP-conjugated melanoma cells in place of DNP-conjugated melanoma cells in order to have provided an effective means for treating melanoma.

Rejections under 35 U.S.C. 103 of claims 1 and 32 as unpatentable over Berd (1989) in view of Fujiwara, over Berd (1990) in view of Fujiwara and over Murphy (1990) in view of Fujiwara

In the response, Applicants traverse this rejection by stating that there is no motivation to combine the cited references and no reasonable expectation of success. However, the teachings of Fujiwara provide the motivation to combine the cited references because Fujiwara teaches that TNP-conjugated tumor cells provide the advantage of augmenting immunity and enhancing the tumor rejection response.

Further, it is again pointed out that while Fujiwara exemplifies methods of vaccination using TNP-conjugated tumor cells to treat mouse leukemia or plastmacytoma cells, the teachings of Fujiwara are not in fact limited to only the treatment of these two types of cancer.

Additionally, given the high level of structural similarity between the DNP and TNP haptens, the ordinary artisan would have had more than a reasonable expectation of success of using TNP in place of DNP. Applicants specification and previous arguments support the conclusion that TNP is an obvious variant of DNP. The present specification does not provide any data for TNP-conjugated melanoma vaccines or AED-conjugated melanoma vaccines and Applicants have clearly not established any improved, or unexpected results obtained when using TNP in place of DNP. The teachings in the specification regarding TNP and AED are limited to a single sentence of: "Other useful haptens include TNP and AED which may be chemically linked to the tumor cells" (see column 3, lines 58-59 of '551). In addressing the enablement of the present invention, Applicants previously argued in the March 6, 1992 response of '551 that "Other haptens of the claimed invention, trinitrophenyl and N-iodoacetyl-N'-(5 sulfonic 1-naphthyl) ethylene diamine, would be expected to behave similarly to DNP" and conclude that the selection and use of alternative haptens, such as TNP, would have been well within the skill of the art. The specification has not established any unexpected results associated with the use of TNP and has acknowledged the obviousness of using alternative haptens with the expectation that they will behave similarly to DNP. Accordingly, the ordinary artisan also recognizing the similarity in structure between DNP and TNP and the ordinary artisan appraised of the teachings of Fujiwara of the use of TNP as a hapten to augment the immune response to tumors, would have been motivated to have used, and would have had more than a reasonable

expectation of success at using TNP-conjugated melanoma vaccines for the treatment of melanoma.

Therefore, the rejections are maintained because the combined references when considered as a whole provide both the motivation and a reasonable expectation of success of using TNP-conjugated melanoma vaccines in place of DNP-conjugated melanoma vaccines for the treatment of cancer.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47, 65-67, 69-72, 74-77 of copending Application No. 08/203,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '004 recite a method of treatment using a composition comprising each of the components of the presently claimed vaccine. In particular, the claims of '004 recite a method using a composition comprising autologous melanoma cells conjugated to a hapten, and mixed

with an immunological adjuvant, wherein the hapten is TNP or AED and the adjuvant is BCG. The claims of '004 recite that the cells have been rendered incapable of growing in the body of a human upon rejection therein, whereas the present claims specify that the cells are irradiated. However, the specification of '004 (page 12) states that "(t)umor cells or extracts are irradiated at 2500 cGy to prevent the cells from growing after injection." Since the claims of '004 are read in light of the specification, it is clear that the claims of '004 encompass irradiated melanoma cells. Accordingly, the claims of '004 disclose a composition comprising each of the components of the presently claimed vaccine and thereby render the presently claimed vaccine obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments:

In the response filed November 18, 2005, Applicants state that a terminal disclaimer will be filed "if the claims of the reissue application still raise a double-patenting issue for the Examiner."

Applicant's response has been fully considered. It is noted that the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained for the reasons of record.

16. Claims 2 and 21-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47, 65-72, 74-77 of copending Application No. 08/203,004 in view of Berd (1988). Although the conflicting claims are not identical, they are not patentably distinct from each other

because both the present claims and the claims of '004 recite vaccines and a method of treatment using a vaccine, wherein the vaccine comprises autologous melanoma cells conjugated to a hapten, and mixed with the immunological adjuvant. In particular, the hapten is DNP, TNP or AED and the adjuvant is BCG (i.e., an immunomodulating agent). The present claims and the claims of '004 also both encompass methods in which the cyclophosphamide is administered to the patient prior to administering the melanoma vaccine. The claims of '004 recite that the cells have been rendered incapable of growing in the body of a human upon rejection therein, whereas the present claims specify that the cells are irradiated. However, the specification of '004 (page 12) states that "(t)umor cells or extracts are irradiated at 2500 cGy to prevent the cells from growing after injection." Since the claims of '004 are read in light of the specification, it is clear that the claims of '004 encompass irradiated melanoma cells. The claims of '004 differ from the present claims in that they do not recite that the vaccine is injected intradermally or that the injection was made to 3 sites on an upper arm or leg.

However, Berd (1988) teaches methods of immunotherapy for human melanoma wherein 10-25 x 10^6 autologous melanoma cells mixed with BCG are injected intradermally into three sites on the patients upper arm or legs (see page 340, column 1). Berd reports that patients receiving CY and the melanoma vaccine developed DTH to tumor antigens (page 342, column 2). Three of the patients tested showed complete remission, one partial remission and two had minor responses to the vaccine (page 344, column 2). According, it would have been obvious to one of ordinary skill in the art at the

time the invention was made to have practiced the method of '004 by injecting the hapten conjugated melanoma vaccine mixed with BCG intradermally to 3 contiguous sites on the patient's upper arm or leg because as taught by Berd (1988) this is a conventional means for administering the melanoma cancer vaccine and would have provided an effective route of administration.

With respect to claims 24, 25, 28 and 29, the claims of '004 do not specifically recite administering the vaccine to post-surgical melanoma patients or to stage 4 melanoma patients. However, Berd (1988; see, e.g., page 340) teaches administering melanoma vaccines to patients post-surgically and to patients with extensive metastatic disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered the hapten-conjugated melanoma to patients post-surgically and to stage 4 melanoma patients in order to have provided an effective means of treatment for those patients most in need of therapy.

With respect to claim 30, the claims of '004 do not specifically recite administering the vaccine every 4 weeks. However, Berd (1988; page 340) teaches repeating the vaccine treatment every 28 days, for up to 15 cycles of administration. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have intradermally administered the hapten-conjugated melanoma vaccine every 4 weeks because this would have boosted the response to the vaccine and thereby would have increased the effectiveness of the therapy.

With respect to claims 21, 22 and 31, the claims of '004 do not recite that the melanoma cells are cryopreserved. However, Berd (1988; page 340) teaches that the

tumor masses are removed from the patient and tumor cells are cryopreserved in liquid nitrogen until needed. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used cryopreserved autologous melanoma cells in the method and compositions of '004 because this would have provided a more convenient means of administering the therapy since such cells could be frozen and stored and then administered at 4 week intervals.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments:

In the response filed November 18, 2005, Applicants state that a terminal disclaimer will be filed "if the claims of the reissue application still raise a double-patenting issue for the Examiner."

Applicant's response has been fully considered. It is noted that the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained for the reasons of record.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENT TO THE CLAIMS:

17. Claims 32 and 33 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought. The added material which is not supported by the prior patent is as follows:

The specification as originally filed does not appear to provide basis for the recitation in newly added claims 32 and 33 of a vaccine which further comprises an immunomodulating drug, particularly wherein the drug is IL-2.

In the response of November 18, 2005, Applicants point to col. 4, lines 4 and 5 of patent 5,290,551 as providing support for this amendment. However, the '551 patent states that "It has been found that administration of an immunomodulating drug, such as IL2, further enhances the efficacy of the present invention. In this embodiment, IL2 is given following the vaccine injection." Accordingly, the '551 patent provides support for the concept of administering the vaccine and then separately administering an immunomodulating drug, such as IL2. However, the '551 patent does not provide support for the concept of a vaccine which contains each of the hapten-conjugated melanoma cells, BCG and an immunomodulating drug such as IL-2.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide basis for the recitation in newly added claims 32 and 33 of a vaccine which further comprises an immunomodulating drug, particularly wherein the drug is IL-2.

In the response of November 18, 2005, Applicants point to col. 4, lines 4 and 5 of patent 5,290,551 as providing support for this amendment. However, the '551 patent states that "It has been found that administration of an immunomodulating drug, such as IL2, further enhances the efficacy of the present invention. In this embodiment, IL2 is given following the vaccine injection." Accordingly, the '551 patent provides support for the concept of administering the vaccine and then separately administering an immunomodulating drug, such as IL2. However, the '551 patent does not provide support for the concept of a vaccine which contains each of the hapten-conjugated melanoma cells, BCG and an immunomodulating drug such as IL-2.

19. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,290,551 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

20. Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
December 21, 2005

CARLA J. MYERS
PRIMARY EXAMINER